UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,342	11/20/2003	Francisco J. Cifuentes	10030679-1	1237

7590 11/05/2007

AGILENT TECHNOLOGIES, INC.
Legal Department, DL429
Intellectual Property Administration
P.O. Box 7599
Loveland, CO 80537-0599

EXAMINER	
SKIBINSKY, ANNA	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
11/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,342	CIFUENTES ET AL.	
	Examiner	Art Unit	
	Anna Skibinsky	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 20-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 20-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment and request for reconsideration in the communication filed on 8/21/07 are acknowledged and the amendments entered.

Claims 1-11 and 20-26 are currently pending and under consideration.

Upon further consideration the allowability of claims 9-11 is withdrawn in view of below rejection.

Specification

The objection to the specification is withdrawn in view of Applicant's amendments filed 8/21/2007.

Claim Rejections - 35 USC § 112

The rejection of claims 2-5 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendments filed 8/21/2007.

Claim Rejections - 35 USC § 102

This rejection is maintained from the previous Office Action filed 5/22/2007.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-4, and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonaventure et al. (Brain Research, Vol. 943, Pages 38-47, July, 2002).

The claims are drawn to a method of selecting a combination of nucleic acid sample pairs comprising:

(a) conducting differential expression experiments using nucleic acid sample pairs and nucleic acid probes immobilized on a substrate

(b) selecting a nucleic acid sample pair by maximizing the number of differentially expressed genes

(c) selecting combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

Bonaventure et al. disclose carrying out differential expression experiments where they look for genes enriched in various brain nuclei using cDNA microarrays (abstract). Given that they see differential expression, the various brain nucleic must comprise different nucleic acid samples. From these experiments, they select locus coeruleus (LC) for discussion in the paper where these nuclei have the maximum number of enriched (or differentially expressed) genes (page 42, 1st column, 3rd paragraph, lines 9-10). As recited in claim 1, step (c), Bonaventure et al. further teach

selecting nucleic acid sample pairs wherein Bonaventure discloses selecting a combination of nucleic acid sample pairs in selecting the locus coeruleus samples for discussion in their paper (page 42, 1st column, 3rd paragraph, lines 9-10) wherein these "selected" samples have the maximized number of differentially expressed genes (table 1) and, since the same genes are monitored for all of the samples, and genes are either differentially expressed or not, by having the maximum number of differentially expressed genes, they also have the minimum number of genes that do not exhibit differential expression.

With respect to claim 2, Bonaventure et al. disclose using intensities for each gene (page 40, 1st column, 2nd paragraph, lines 11-14) and calculating a median value across probes (page 40, 1st column, 2nd paragraph, line 16) and determining the statistical significance of the spread in values (page 40, 1st column, 2nd paragraph, lines 16-20) thereby determining whether they probe values cluster.

With respect to claims 3 and 4, Bonaventure et al. disclose using the raw signal intensities to produce log-treated values (page 40, 1st column, 2nd paragraph, line 20).

With respect to claim 6, Bonaventure et al. carry out a plurality of differential gene expression experiments using a plurality of experimental sets in using a plurality of cellular nuclei (see table 1).

With respect to claims 7-8, Bonaventure et al. disclose that each sample is hybridized to a separate substrate (page 40, 1st paragraph, line 3), as in claim 8, and, in the process of being hybridized to separate substrates they are being hybridized to a substrate, as in claim 7.

Response to Arguments

Applicant's arguments filed 8/21/2007 have been fully considered but they are not persuasive.

This rejection is modified from the rejection in the Office action mailed 11/22/06. The modification was necessitated by applicants' amendments. Applicants' arguments have been fully considered, but they are not found persuasive.

Applicants argue (Remarks, page 8, ¶ 6-7 and page 9, ¶2) that Bonaventure does not teach the limitation of claim 1 step (c), wherein there is no discussion in the prior art of selecting a combination of nucleic acid pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

In response, the instant limitation is taught as shown in Table 1, wherein expressed genes containing the nucleic acid pairs are listed and counted and have therefore been "selected". The genes in Table 1 (page 42, col. 1) are those that were evaluated using cDNA array of probes and differentially expressed (pages 39-40, section 2.5 cDNA microarray).

For the reasons stated above Applicant's arguments are not persuasive and are maintained for reasons of record.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 9 is rejected under 35 U.S.C. 103(a) as being obvious over Bonaventure et al. (Brain Research, Vol. 943, Pages 38-47, July, 2002) in view of Li et al (Bioinformatics, vol. 17 (2001) 1067-1076).

Bonaventure et al. disclose carrying out differential expression experiments where they look for genes enriched in various brain nuclei using cDNA microarrays (abstract). Given that they see differential expression, the various brain nucleic must comprise different nucleic acid samples, as in claim 9 steps (a) and (b). From these experiments, they select locus coeruleus (LC) for discussion in the paper where these nuclei have the maximum number of enriched (or differentially expressed) genes (page 42, 1st column, 3rd paragraph, lines 9-10). As recited in claim 9, steps (c) and (e), Bonaventure et al. further teach selecting nucleic acid sample pairs wherein Bonaventure discloses selecting a combination of nucleic acid sample pairs in selecting the locus coeruleus samples for discussion in their paper (page 42, 1st column, 3rd

paragraph, lines 9-10) wherein these "selected" samples have the maximized number of differentially expressed genes (table 1), a required in claim 9, step (c) "tabulating" and since the same genes are monitored for all of the samples, and genes are either differentially expressed or not, by having the maximum number of differentially expressed genes, they also have the minimum number of genes that do not exhibit differential expression.

Bonaventure et al. does not teach assigning "a yes value" or "a no value" for a gene that exhibits differential expression or does not exhibit differential expression, respectively, as required in claim 9, step (c).

Li however teaches an algorithmic method of comparing a probe sequence and its compliment on genome sequences (Abstract). For complimentary bases, a matrix value of '1' is assigned (i.e. "a yes value") otherwise, for non-complimentary bases, a matrix value of '0' is assigned (i.e. "a no value"), as required in step (c). In another embodiment, the matrix can be interpreted to the mechanism for tabulating as required in claim 9, step (d) (page 1070, col. 2, ¶ 2). Probes that match the genome sequence are then selected (page 1070, col. 2, ¶ 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the computerized method of Bonaventure et al. for determining differential expression in genes and selecting nucleic acid pairs from a plurality of samples as taught by Bonaventure et al. with the method of assigning a "yes value" in the form of a "1" and a "no" value in the form of a "0" when probes are complementary to sections of a genome as taught by Li et al. One of skill in

the art would have been motivated to combine the method of Li et al. with that of Bonaventure et al. because Li et al. suggest that this algorithm is a fast method for comparing every potential probe in every gene with all possible target sites in the genome (page 1070, col. 2, ¶ 3). One of skill in the art would have had a reasonable expectation of success at combining the method of Bonaventure et al. with that of Li et al. because both teach computerized methods for selecting optimal DNA oligonucleotides and Li et al. suggest that their algorithm is adaptable to other applications (page 1070, col. 2, ¶ 2).

Claims 10-11 are rejected under 35 U.S.C. 103(a) as being obvious over Bonaventure et al. (Brain Research, Vol. 943, Pages 38-47, July, 2002) in view of Li et al. (Bioinformatics, vol. 17 (2001) 1067-1076), as applied to claim 9 above, and in further view of Huber et al. (Bioinformatics vol. 18 Supplement (2002) pages 96-104).

Bonaventure et al. in view of Li et al. make obvious a method of selecting nucleic acid pairs for evaluating the ability of oligonucleotide probes to measure differential expression of genes by assigning "a yes value" or "a no value" for a gene that does or doesn't exhibit differential expression, as set forth above. Bonaventure et al. in view of Li et al. do not teach parameters selected from the group of LogRatio, LogRation error, as in claim 10, and intensity and wherein the nucleic acid sample pairs are tissue pairs, as in claim 11.

Huber et al. teach the quantification of differential expression using variance calculation and the log ratio of intensities for microarray gene expression data (Abstract

and page 97, col. 1, ¶4). Huber et al. teach genes taken from tissue sample (page 96, col. 1, ¶ 1) and paired samples from cancerous patients (page 100, col. 2, ¶2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the method of Bonaventure et al. in view of Li et al. for selecting nucleic acid pairs with that of Huber et al. for quantifying differential expression of genes from tissue using the log ratio. One of skill in the art would have been motivated to use the method of Huber et al. with that made obvious by Bonaventure et al. and Li et al. because Huber et al. teach that their method overcomes limitations of previous methods (page 97, col. 1, ¶3-4) and provides a basis for statistical inference and multivariate analysis (Abstract). One of skill in the art would have had a reasonable expectation of success at utilizing the method of Bonaventure et al. in view of Li et al. with that of Huber et al. because all three teach measurement of differential expression using algorithmic computational methods.

Claims 1-8 and 20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. (US Patent Publication #2004/0101845, filed November 22nd, 2002) in view of Hosaka et al. (Genome Informatics, vol. 12 (2001) 449-450; listed in IDS).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are drawn to a method of selecting a combination of nucleic acid sample pairs comprising:

(a) conducting differential expression experiments using nucleic acid sample pairs and nucleic acid probes immobilized on a substrate

(b) selecting a nucleic acid sample pair by maximizing the number of differentially expressed genes

(c) selecting a combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

Collins discloses selection of nucleic acid sample pairs by hybridizing nucleic acid sample pairs to nucleic acids on microarrays and selecting for those sample pairs that maximize the number of mRNAs that are differentially expressed (paragraphs 70-72). Since Collins is detecting differential expression, the different pairs must comprise different nucleic acid samples. Collins teaches the "employing" the consensus region of two or more mRNA transcripts to identify the suitable nucleic acid sequence for use as a probe (Abstract). After the probe array is contacted with the sample, hybridization is detected. Since the transcript gene (mRNA) under consideration is known (paragraph 84).

With respect to claim 2, Collins discloses evaluating each probe (representative of genes) and clustering based upon evaluation of differential expression (see, for example, paragraphs 51,52).

With respect to claims 3-4, Collins discloses consideration of the parameter of LogRatio in determining differential expression (for example, paragraph 71).

With respect to claim 5, Collins discloses that the parameters include probability of significant difference and number of probes of significant difference (paragraph 99, lines 8-10).

With respect to claim 6, Collins discloses that the sample pairs are tissue pairs (paragraph 70, lines 6-8).

With respect to claims 7-8, Collins discloses contacting sample pairs with either a single substrate or separate substrates (paragraph 69).

With respect to claim 20, Collins discloses evaluating candidate probes using sample pairs identified through the method of claim 1 (see paragraph 69).

With respect to claim 21, Collins discloses the method (claim 1) where Collins has previously defined that the evaluation employs a nucleic acid sample pair selected by the method of claim 1 (as cited for claim 20).

With respect to claim 22, Collins discloses the method (see, for example, claims 18 or 19).

With respect to claim 23, Collins discloses the method (see, for example, paragraph 116).

With respect to claim 24, Collins discloses the method (see, for example, paragraph 116, lines 30-33).

With respect to claim 25, Collins discloses the method (see, for example, paragraph 115).

With respect to claim 26, Collins discloses the method (see, for example, paragraph 116, lines 32-33).

Collins et al. does not however teach "selecting" a combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

Hosaka et al. does teach and algorithmic method for evaluating gene expression patterns and selecting regions of genes as candidates for the probes (page 449, ¶ 3 and ¶ 7)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the method of Collins et al. for conducting differential expression experiments with the method of Hosaka for selecting gene regions as candidates for probes. One of skill in the art would have been motivated to combine the method of Collins et al. with that of Hosaka et al because Hosaka et al. teach that examining gene expression patterns is one of the fundamental methods for examining organisms at the molecular level (page 449, ¶1). One of skill in the art would have had a reasonable expectation of success at utilizing the method of Collins et al. with that of Hosaka et al. because both teach computerized algorithms for probe design.

Response to Arguments

Applicant's arguments filed 8/21/2007 have been fully considered but they are not persuasive.

Applicants argue (Remarks, page 10, ¶ 4) that Collins discusses a method for identifying candidate probes for a target nucleic acid and not a method for selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

In response, it is noted that Collins teaches a method for identifying candidate probes for a target nucleic acid by identifying differential expression of genes on a microarray, thereby selecting the probes. However, Collins in view of Hosaka et al. teach a method of selecting gene pairs for binding with candidate probes, wherein Hosaka et al. measures observes gene expression by probe hybridization and then selects the regions of the genes, as required by the instant claims and pointed to in the above rejection.

7. Claims 20-24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dooley et al. (US Patent Publication # 2001/0046671, Publication Date Nov. 29, 2001) in view of Bonaventure et al. (Brain Research, Vol. 943, Pages 38-47, July, 2002).

The claims are drawn to a method of identifying a sequence of nucleic acid suitable for use as a substrate immobilized probe comprising:

(a) identifying a plurality of candidate probes

(b) empirically evaluating each of the candidate probes using the sample pair of Claim 1

(c) clustering candidate probes into groups

(d) selecting one of the groups

(e) choosing a candidate probe from the selected group

Dooley et al. disclose identifying a plurality of candidate probes that are chosen for their expression in a given sample type (paragraph 12, lines 11-14). They empirically evaluate these probes against a specified sample for which they are specifically designing the probes (Fig. 1, II, 3). They disclose clustering of probe sequences (Fig. 1, III, 4), selecting those that are relevant to the desired application (Fig. 1, IV, 1) and then specifically choosing examples that are appropriate (fig. 1, IV, 2-4), as required by claims 20 and 21. With respect to claim 20, claim 21 represents a species of claim 20 and thus since Dooley et al. discloses the method of claim 21, they makes obvious the method of claim 20.

With respect to claim 22, the combination of Dooley et al. disclose the method of claim 21 for identifying nucleic acid probes (as cited above), and Dooley et al. disclose synthesizing and depositing said probes in an array on a substrate (for example, fig. 1, IV, 4).

With respect to claim 23, Dooley et al. disclose contacting the produced array with a sample and detecting the presence of complexes (for example, fig. 1, V, first bullet, and references therefrom).

With respect to claims 24 and 26, Dooley et al. disclose forwarding data from a detector where the data in then received by a computer (paragraph 8, lines 14-17).

However, Dooley et al. do not disclose using a sample pair from claim 1.

Bonaventure et al. disclose carrying out differential expression experiments where they look for genes enriched in various brain nuclei using cDNA microarrays (abstract). Given that they see differential expression, the various brain nucleic must comprise different nucleic acid samples. From these experiments, they select locus coeruleus (LC) for discussion in the paper where these nuclei have the maximum number of enriched (or differentially expressed) genes (page 42, 1st column, 3rd paragraph, lines 9-10).

It would have been obvious, for one of ordinary skill in the art, at the time the invention was made, to modify the method of Dooley et al. to use it in combination with the method of Bonaventure et al. to test Dooley's probes with the tissue pair of Bonaventure et al. One of ordinary skill in the art would have been motivated to do this because, as suggested by Dooley et al., by designing an "informative array" using the combination, one could enhance the ability to identify differentially expressed genes (paragraph 19, lines 4-8).

This rejection is maintained from the previous Office action mailed 11/22/06.

Response to Arguments

Applicant's arguments filed 8/21/2007 have been fully considered but they are not persuasive.

Applicant's arguments (Remarks, page 12, ¶ 2-3) against the obviousness rejection of Dooley in view of Bonaventure rely on the failure of the Bonaventure reference to anticipate claim 1. As such, having rebutted the arguments against Bonaventure as applied to claim 1 in the 102(b) rejection above, the arguments against Dooley in view of Bonaventure are rebutted as well.

Double Patenting

The obviousness type double patenting rejection of claims 20-22 and 102(f) rejection of claims 20-22 in the Office Action filed 5/22/2007 are withdrawn.

Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8:30 AM - 5:00 PM M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anna Skibinsky, PhD
Art Unit 1631

Marjorie A. Moran
SPE, AU 1631
10/29/07